Thrombotic Microangiopathies In Kidney Transplantion

Dr. Mohamed Sobh MD, FACP
Professor Of Neprology-Urology&Nephrology Center
Director Of Medical&Experimental Research Center
Mansoura Faculty Of Medicine

Thrombotic Microangiopathies

- Thrombotic microangiopathy (TMA) is characterized by an acute syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and variable signs of organ injury (iscaemic)due to platelet thrombosis in the microcirculation.
- Depending on the predominant distribution of the lesions—kidney or central nervous system (CNS)—two pathologically identical but clinically distinct entities are described: hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).
- HUS usually affects young children and is characterized by acute kidney injury (AKI) and absent or minimal neurologic abnormalities.
- TTP occurs in adults and is characterized by severe neurologic involvement in most cases and variable renal involvement.
- In some patients, features of HUS and TTP may coexist

- Haemolytic uraemic syndrome is a frequent cause of renal failure in children.
- Most cases are diarrhoea-associated (D+ HUS) and are usually related to exotoxins produced by Escherichia coli O157:H7.
- Other cases are not associated to diarrhoea (D- HUS).
- Rarely, HUS may occur in several members of the same family (familial HUS) with an autosomal dominant or recessive inheritance. In these cases, the disease may present in neonatal age or in the adulthood.
- About 30% to 50% of D- HUS have mutations in one of the complement control proteins: factor H, factor I or membrane cofactor protein (MCP)

Classification of Thrombotic Microangiopathies

TMA associated with infectious disease
- Shigatoxin-associated HUS
- Neuraminidase (pneumococcal)-associated TMA
- HIV infection

TTP associated with genetic or immune-mediated ADAMTS13 abnormalities

HUS associated with genetic or immune-mediated abnormalities of the complement system
- Genetically determined factor H deficiency
- Genetic membrane cofactor protein abnormalities
- Complement factor I deficiency
- Gain-of-function mutations of complement factor B
- Complement C3 mutations
- Immune-mediated factor H deficiency

Pregnancy-associated TMA
- TTP
- HELLP syndrome
- Postpartum HUS

Systemic disease-associated TMA
- Antiphospholipid, scleroderma, malignant hypertension
- Malignancy

Drug associated

Transplant associated
- *De novo* HUS
- Recurrent post-transplantation HUS

Kidney Transplantation–Associated Hemolytic-Uremic Syndrome

- HUS may develop *de novo after transplantation or* may recur in patients whose primary cause of ESRD was HUS.
- The time from transplantation to diagnosis of TMA is variable; it has been reported to be between few days to years after transplantation, suggesting that different mechanisms are involved.

De novo post-transplant TMA

- The reported incidence of de novo TMA in kidney transplants varies considerably.
- In the analysis of USRDS data,a de novo TMA was reported in only 0.8% of cases.
- However, this rate may be underestimated as single-centre studies reported an incidence ranging between 4% and 14%.
- A number of factors may increase the risk of developing a TMA in transplanted kidneys.
- They include marginal kidneys , cytomegalovirus infection, parvovirus B 19 infection , BK polyoma virus nephritis ,antiphospholipid antibodies, anticardiolipin antibodies ,in HCV-positive patients or malignancy.
- Rarely, drugs such as valacyclovir or clopidogrel may also cause TMA.
- However, the most important risk factors are by far represented by cyclosporin and tacrolimus , as well as by anti-mTOR drugs.

- Vasoconstriction due to a reduction of both prostacyclin synthesis and prostacyclin-to thromboxane A2 ratio, decreased generation of activated protein C, increased production and release of high-molecular- weight VWF multimer from endothelial cells, endothelial toxicity and its pro-thrombotic and antifibrinolytic activity, all enhance leukocyte adhesion to vascular endothelium,and release of thromboplastin from mononuclear cells. All these factors are proposed mechanism for CsA-induced TMA.
- Concomitant ischemia-reperfusion and its deleterious effect on endothelium, and higher dosage of CsA further augment the deleterious effects of CsA
- mTOR inhibitors may act as a subsequent aggressor, as it has been demonstrated that sirolimus may induce down regulation of vascular endothelial growth factor, which is required for repairing CNI nephrotoxicity and TMA.

- Renal ischemia by it self is an initiating event for development of TMA.
- Prolonged ischemia is a pro-apoptotic factor and endothelial cells acquire pro-coagulant properties upon activation of apoptosis.
- After reperfusion, contact between apoptotic microvascular endothelial cells and blood constituents, causes activation of platelets and occurrence of TMA alongside with ATN during renal transplantation without significant independent association between HLA mismatch and recipient sensitization.

Thrombotic thrombocytopenic purpura associated with everolimus use in a renal transplant patient

Vural Taner Yilmaz · Hüseyin Koçak · Ali B. Avci · Ozan Salim · Fevzi F. Ersoy · Gültekin Süleymanlar

Received: 18 October 2009 / Accepted: 3 May 2010 / Published online: 22 May 2010

Abstract Thrombotic microangiopathy (TMA) in renal transplantation (RTX) generally develops during treatment with calcineurin inhibitors. We present a RTX case that developed TMA under everolimus treatment. A 40-year-old woman received a kidney allograft from her 77-year-old mother. She initially received tacrolimus, mycophenolate mofetil and steroids. She was discharged with a creatinine level of 2.2 mg/dl after treatment for a cellular rejection attack within the first two weeks after transplantation. Later on, tacrolimus was replaced with everolimus. One year later, she presented with fever and increased creatinine level (4 mg/dl), anemia and thrombocytopenia. Her peripheral blood smear revealed signs of microangiopathic hemolysis. Bone marrow examination revealed an increased number of megakaryocytes. We diagnosed the case as TMA and initiated plasma exchange, I.V. pulse steroid treatment and stopped everolimus. This approach improved laboratory and clinic abnormalities. The development of TMA after treatment with everolimus and the exclusion of other possible causes suggested TMA associated with proliferating signal inhibitors (PSIs) in our case.

Keywords Everolimus · Thrombotic microangiopathy

V. T. Yilmaz (✉) · H. Koçak · A. B. Avci · O. Salim · F. F. Ersoy · G. Suleymanlar
Akdeniz University Hospital, Antalya, Turkey
e-mail: vuralcavcyl@yahoo.com.tr

Introduction

Thrombotic microangiopathy can be seen in 3–14% of RTX recipients. Predisposing factors include calcineurin inhibitor (CNI) treatment, female sex, infections, and hereditary factors [1, 2]. It may develop just after transplantation as a recurrence or it may occur de novo later on. Hemolysis, thrombocytopenia, neurological symptoms and acute renal failure are the most frequent manifestations in these cases. Additionally, hemoglobinuria, hemoglobinemia, an elevation of serum lactate dehydrogenase, a decrease of serum haptoglobin and fragmentation of erythrocytes on blood smear commonly accompany these findings [3].

TMA is frequently associated with CNIs treatment, among other immunosuppressive drugs [4]. Cyclosporine is particularly prone to cause TMA by vasoconstriction, increase in prothrombotic activity and endothelial damage. TMA associated with m-TOR inhibitors is rare, and the mechanism is not clear, but it may trigger TMA especially in patients with a high risk of endothelial damage (e.g. with marginal donors, or those receiving a combination with CNIs) [5, 6]. Sirolimus is also postulated to cause TMA by decreasing the expression of vascular endothelial growth factor [7].

Post-transplant TMA can be controlled in up to 80% of patients with dose reduction or cessation of calcineurin inhibitors, switching to sirolimus, plasma exchange and I.V. pulse steroid treatment [2, 8]. In

- Acute vascular rejection that damages the endothelial cells should always be considered in the differential diagnosis of post-transplant TMA, in particular when tubules and interstitial infiltration are accompanied by severe endo-vasculitis affecting entire renal allograft vasculature.
- Distinguishing between post-transplant TMA and acute vascular rejection is extremely difficult on clinical grounds; it is confirmed only on renal biopsy. Both cases are associated with acute renal failure, microangiopathic hemolytic anemia and thrombocytopenia.

- Viruses, particularly CMV infection, influenza A, parvovirus B-19, HIV, and HHV-6, and anti-cardiolipin antibody positivity in a subset of hepatitis C virus are reported as triggers of TMA.
- Patients with parvovirus B-19 infection present with fever, fatigue,arthralgia, aplastic anemia, thrombocytopenia,and deterioration of renal function about 15-20 days after renal transplantation.

- Exposure to agents that are toxic to the vascular endothelium, such as viruses, bacteria, immune-complexes, auto-antibodies and cytotoxic drugs, could initiate a local intravascular thrombosis.

Recurrent Post-Transplantation Hemolytic-Uremic Syndrome

- Kidney transplantation is effective and safe for those children with Stx-HUS who progress to ESRD.
- The recurrence rates range from 0% to 10%, and graft survival at 10 years is even better than in pediatric transplant recipients with other primary renal disease.
- Mutations in circulating complement factors H, I, B, and C3, all of which are mainly produced by the liver, will persist after kidney transplantation, resulting in post-transplantation recurrence in 80% of patients with mutations in the gene encoding complement factor F or I. Recurrence rates in patients with complement factor B or C3 mutations are less well established

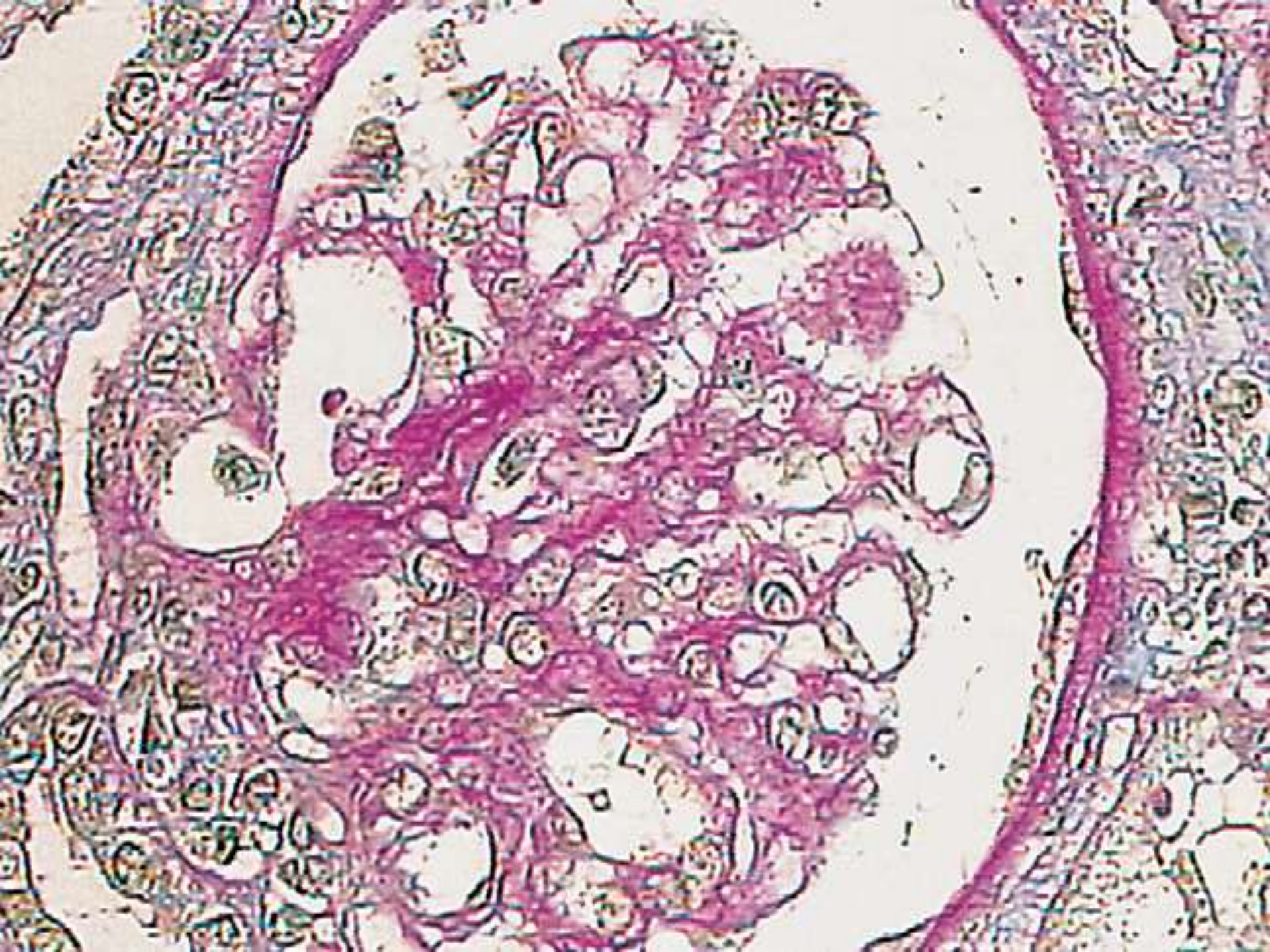
Forms of TMA in native kidneys	Risk of recurrence in transplanted kidneys
Postdiarrhoeal (D+)	Negligible
Nonpostdiarrhoeal (D−).	
Sporadic or familial forms	
Mutation in factor H	80%
Mutation in factor I	80–100%
Mutation in membrane cofactor protein	0%
Idiopathic	33–56%
Secondary to pregnancy, drugs, etc.	Negligible

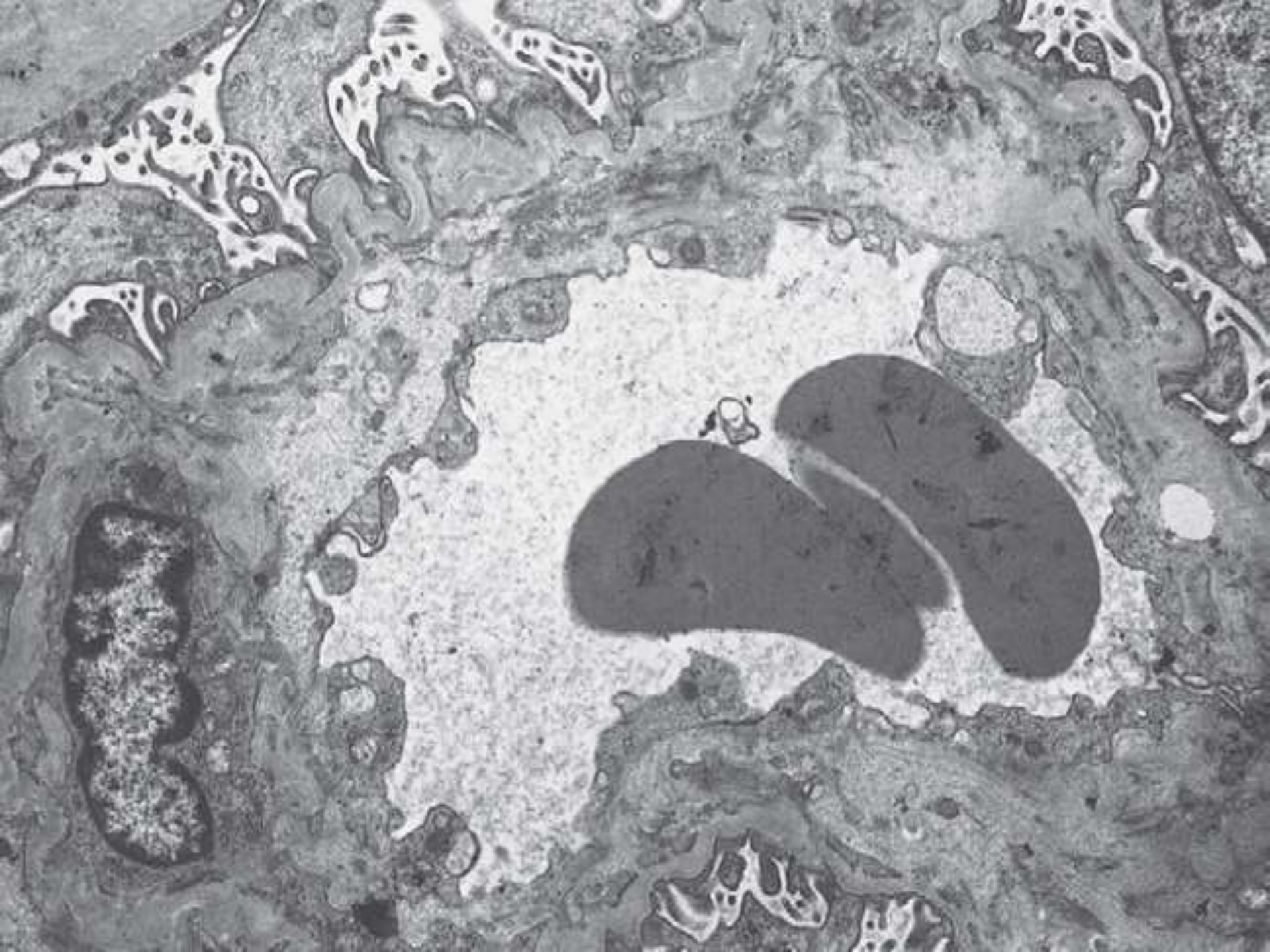
Risk of recurrence of the different forms of thrombotic microangiopathy (TMA) after renal transplantation

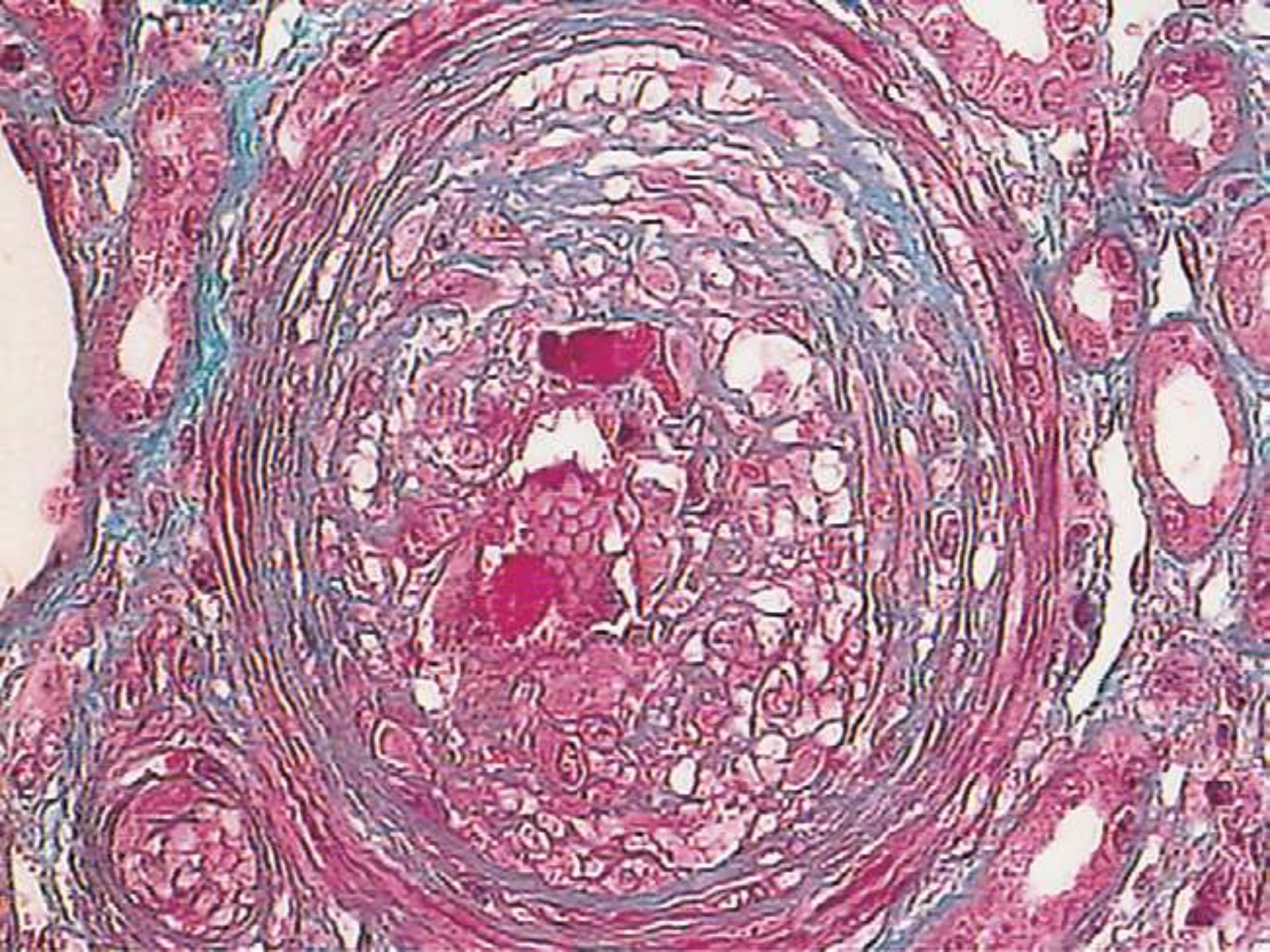
- If the cause of ESRD is HUS/TTP, its recurrence is negligible for childhood type D+HUS and outcome after kidney transplantation is good with recurrence rate ranging from 0 to 10 %.
- In adult type non-Stx-HUS, approximately 50% of renal transplanted patients develop recurrence of the disease in the allograft while the recurrence rate is nearly 100% in familial/recurrent forms with the median time to recurrence being 30 days after transplantation.
- The one-year graft survival is about 80% after childhood, and less than 30%, after adult-onset HUS.
- Living related transplantation is associated with an increased risk of recurrence, probably suggesting a genetic (familial) predisposition, and the possibility that the donor might have a same factor H abnormality.

Pathology

- The characteristic histological lesion of TMA consists of arteriolar wall thickening (capillaries and arterioles), swelling and detachment of endothelial cells from the basement membrane (sub-endothelial space widening), accumulation of fluffy amorphous material in the sub endothelium, ballooning of glomerular lobules, and glomerular ischemia.
- Patchy cortical necrosis may be present in severe cases; crescent formation is uncommon.
- The constituents of arterial thrombi in TTP and HUS include platelet and VWF initially, and fibrinogen and thrombin at later stages.
- Sometimes, the histological findings are indistinguishable from malignant hypertension.







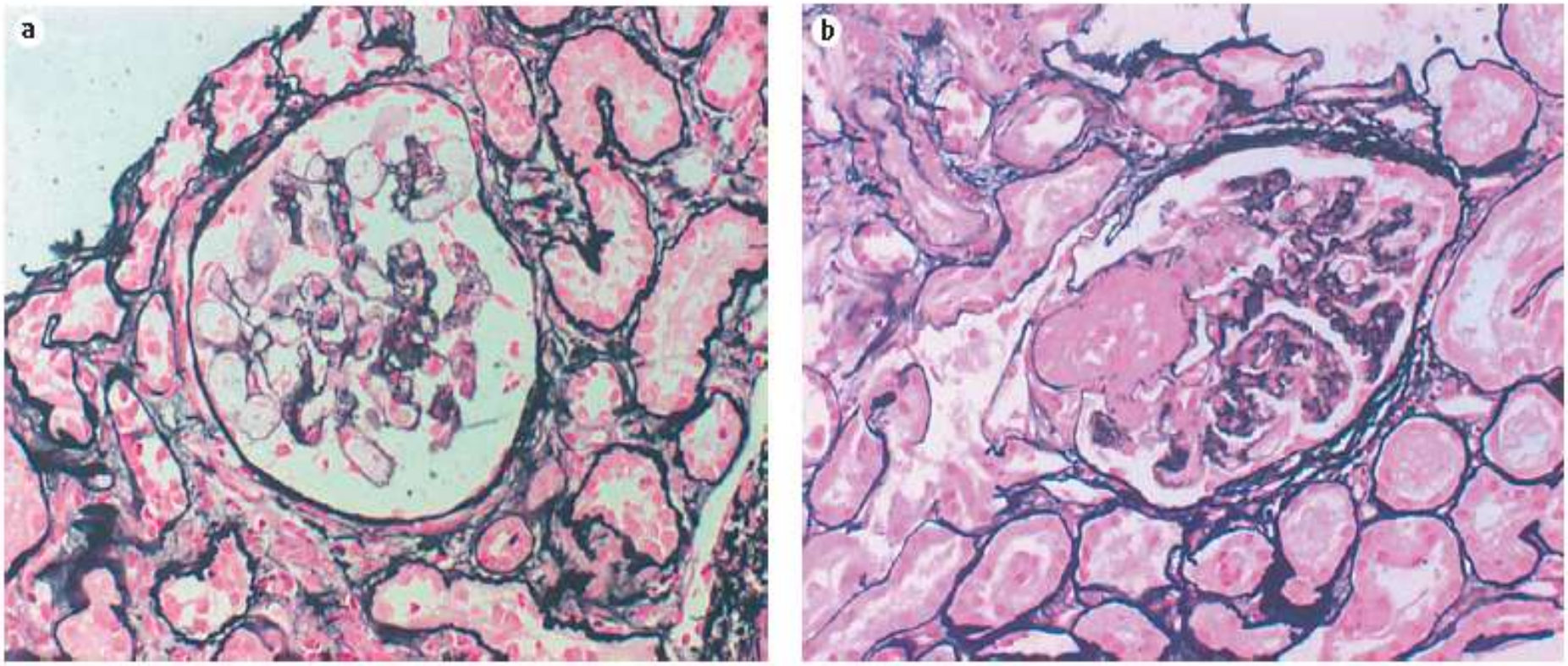
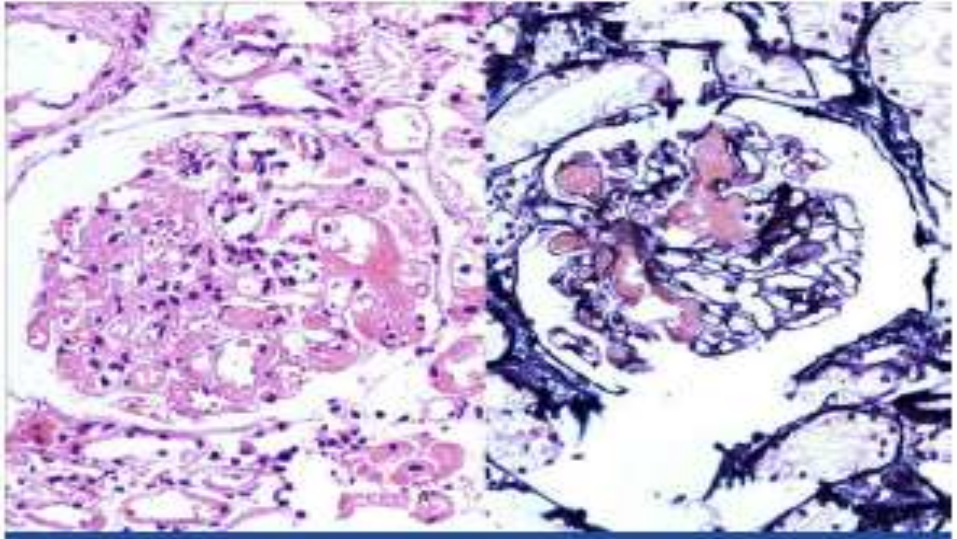
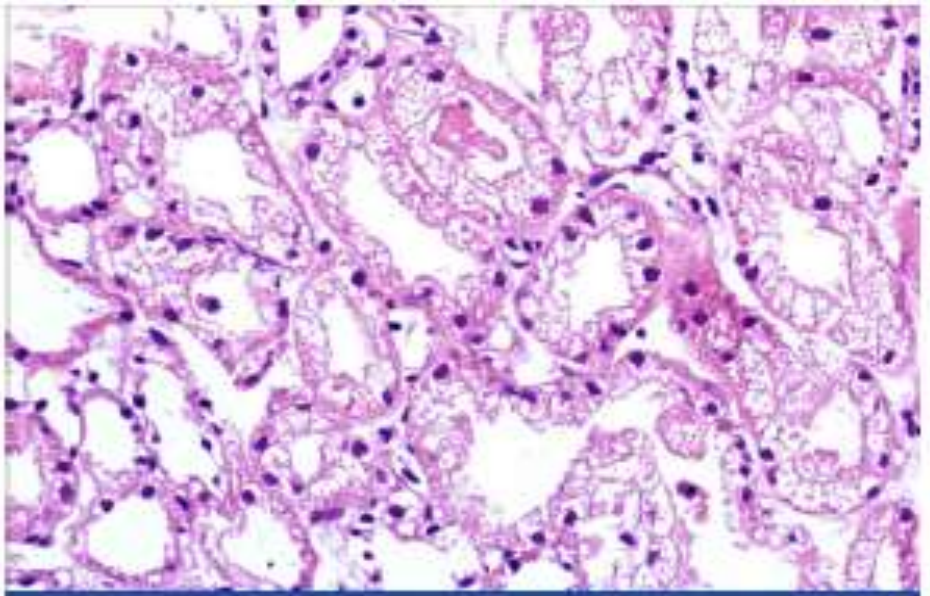


Fig. 1. Renal allograft with CMV-induced posttransplant TMA shows dilated capillary loops with thinning of the capillary walls and subendothelial fibrin deposits (**a**) and an obliterated lumen of the capillary loop by a thrombus (**b**). Methenamine-silver stain. Original magnification ×250.

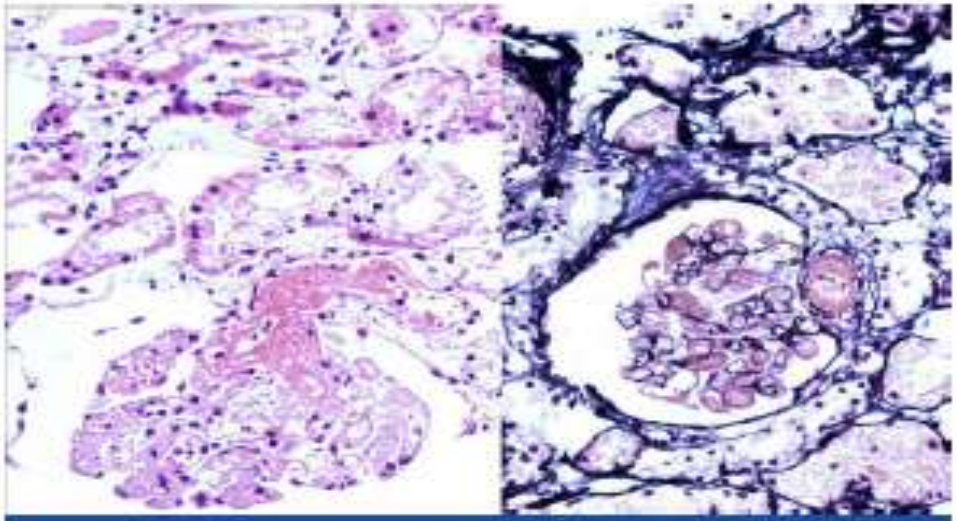


[Table/Fig-1]: (A) Fibrin thrombi in glomerular capillaries, widening of Bowmans space. H&E X 400

(B) Fibrin thrombi in glomerular capillaries, widening of Bowmans space. Silver methenamine X 400

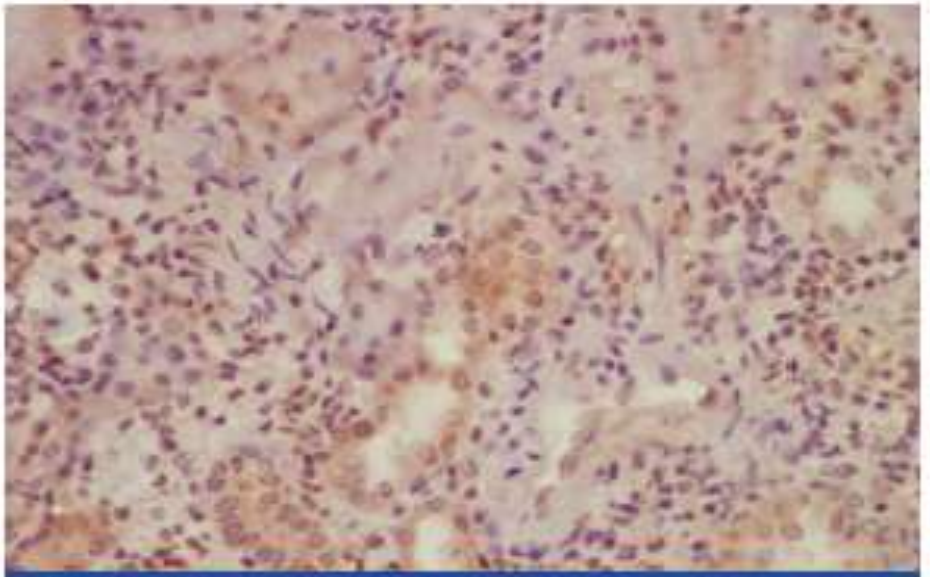


[Table/Fig-3]: Isometric vacuolization of proximal tubular epithelial cell cytoplasm. H&E X 400



[Table/Fig-2]: (A) Fibrin thrombi in glomerular capillaries and arterioles at the glomerular vascular pole. H&E X 400

(B) Fibrinoid necrosis and platelet fibrin thrombus affecting arterioles at glomerular vascular pole. Silver methenamine X 400



[Table/Fig-4]: Immunohistochemistry : C4d not detected along peritubular capillaries. Anti-C4d-horseradish peroxidase X 400

Clinical Presentation

- The time from transplantation to diagnosis of TMA is variable; it has been reported to be between few days to years after transplantation, suggesting that different mechanisms are involved.
- The clinical presentation of post-transplantation TMA is variable; it often manifests clinically as the HUS, with classical findings of renal failure, hemolytic anemia, schiocytes,and thrombocytopenia, with worsening renal function or delayed graft function (DGF).
- Localized TMA presents with worsening renal function, and DGF, with few or no systemic manifestations, thrombocytopenia and anemia.
- Renal dysfunction can be the only finding and acute rejection, CsA and tacrolimus nephrotoxicity, and *Cytomegalovirus*(CMV) infection could confuse the situation.
- The rate of graft loss is strongly influenced by whether the TMA is systemic or renal limited with localized TMA having a better short-term prognosis than systemic TMA.

Prognoses

- The prognosis of recurent TMA is poor.
- The USRDS data reported a patient survival rate of 50% at 3 years.
- In a review, 24 patients had renal transplantation for HUS/TTP, the 2-year graft survival was 35%, but eventually all patients with recurrence lost their allograft , Conlon PJ,1996.
- In another series,the 1-year graft survival in 17 adult patients with TMA recurrence was 29%, while survival in childhood-onset HUS was comparable with matched controls ,Artz MA et al 2003..

- The prognosis of de novo is less severe than with recurrent TMA.
- It may depend on the severity of histological lesions and clinical features.
- Prognosis is more favourable when TMA occurs later in the post-transplant course or when it affects recipients of allografts from living donors.
- Graft loss is rare in patients with TMA localized only to the kidney, while patients with systemic signs and symptoms of HUS are more likely to need dialysis and to lose the allograft function.

Treatment

- Withdrawal of the cause, and treatment of precipitating factors are the most effective approaches.
- Plasma exchange, as the mainstay therapy for TMA confers its effectiveness by replenishing the missing ADAMTS13 and/or removal of its inhibitors.
- Drug withdrawal or dose reduction as first-line therapy for *de novo CsA-or tacrolimus-associated TMA; it* is effective in fewer than 50% of patients although a higher success rate (84%) has been reported with adjunctive plasma infusion or exchange.
- Dose reduction, withdrawal, or conversion from one calcinurin inhibitor to another may result in acute rejection.
- Sirolimus was associated with a good outcome in patients with CsA or tacrolimus associated HUS.
- The outcome of *de novo forms occurring in the* setting of viral infection is strongly influenced by the response to the treatment of the underlying disease.

- Treatment of atypical HUS is disappointing.
- Plasmapheresis or generous plasma infusion may increase the serum levels of factor H/factor I and obtain recovery of thrombocytopenia and microangiopathic anaemia in some patients, but are only rarely effective on preventing renal damage.
- However, prevention of relapses and preservation of renal function have been obtained in a renal transplant child treated with prophylactic plasmaferesis twice weekly (Landau D, el 2001).
- Two transplant patients with life-threatening recurrent HUS resistant to multiple courses of plasma exchanges were rescued by the administration of i.v. immunoglobulins and rituximab respectively.
- In order to restore the defective factor H,combined liver and kidney transplantation has been performed in few patients.

- Other less invasive treatment strategies to prevent recurrence of aHUS after kidney transplantation in patients with factor H mutations include intensified plasma exchange and C5 blockade.
- Intensive plasma exchange given before and long lasting after a single kidney transplantation and followed by chronic weekly plasma infusion prevented HUS recurrences in five of six patients.
- Eculizumab is a humanized monoclonal antibody against complement C5, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of C5b-9It has been approved for the treatment of paroxysmal nocturnal hemoglobinuria and displays an excellent safety profile.
- Eculizumab so far has been given to few patients with aHUS, some of them with recurrent aHUS in a renal allograft.In them , treatment resulted in reversal of hemolysis and partial recovery of renal function.

Liver-Kidney Transplantation to Cure Atypical Hemolytic Uremic Syndrome

Jeffrey M. Saland, Piero Ruggenenti, Giuseppe Remuzzi, and the Consensus Study Group

ABSTRACT

Atypical hemolytic uremic syndrome is often associated with mutations in genes encoding complement regulatory proteins and secondary disorders of complement regulation. Progression to kidney failure and recurrence with graft loss after kidney transplantation are frequent. The most common mutation is in the gene encoding complement factor H. Combined liver-kidney transplantation may correct this complement abnormality and prevent recurrence when the defect involves genes encoding circulating proteins that are synthesized in the liver, such as factor H or I. Good outcomes have been reported when surgery is associated with intensified plasma therapy. A consensus conference to establish treatment guidelines for atypical hemolytic uremic syndrome was held in Bergamo in December 2007. The recommendations in this artide are the result of combined dinical experience, shared research expertise, and a review of the literature and registry information. This statement defines groups in which isolated kidney transplantation is extremely unlikely to be successful and a combined liver-kidney transplant is recommended and also defines those for whom kidney transplant remains a viable option. Although combined liver-kidney or isolated liver transplantation is the preferred therapeutic option in many cases, the gravity of risk associated with the procedure has not been eliminated completely, and assessment of risk and benefit requires careful and individual attention.

J Am Soc Nephrol 20: 940–949, 2009. doi: 10.1681/ASN.2008080906

most cases in association with hom
gous deletion of the genes enco
complement factor H–related prote
and 3 (*CFHR1* and *CFHR3*).[9] In
there is a growing list of the mutat
polymorphisms, and other comple
abnormalities that alone or in com
tion may lead to aHUS.[8–13]

KIDNEY TRANSPLANTATION A
RISK FOR DISEASE RECURREN

Compared with patients with typical
those with aHUS also have worse
comes after kidney transplantation, la
because of the high rates of disease r
rence.[14,15] The disease recurs in nearly
of transplant recipients with *CFH* m
tions, and recurrences are usually as
ated with graft loss.[2,16,17] Although the

American Journal of Transplantation 2009; 9: 420–427
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2008.02482.x

Case Report

Belatacept as Maintenance Immunosuppression for Postrenal Transplant *de novo* Drug-Induced Thrombotic Microangiopathy

N. Ashman[a,*], A. Chapagain[a], H. Dobbie[a], M. J. Raftery[a], M. T. Sheaff[b] and M. M. Yaqoob[a]

Departments of [a]Renal Medicine and Transplantation and [b]Histopathology, The Royal London Hospital, London, UK
**Corresponding author: Neil Ashman, neil.ashman@bartsandthelondon.nhs.uk*

De novo posttransplant thrombotic microangiopathy (TMA) is a complication of solid organ transplantation, which remains difficult to treat. In many cases, immunosuppressants and particularly calcineurin inhibitors, trigger TMA. Although withdrawing the offending drug may lead to resolution of TMA, graft and patient outcomes are poor. Specific treatments, including plasma exchange, have not gained widespread acceptance in those with fulminant disease and new approaches to the condition are urgently needed.

curs most frequently in renal transplantation. This is in part because the hemolytic uremic syndrome (HUS) is a not infrequent cause of end stage renal disease, and familial forms in particular have a high rate of recurrence within renal allografts. TMA is described as *de novo* if the disorder arises after transplantantion in patients with no prior history of TMA.

In the latter group, immunosuppressants are usually implicated in causing or prolonging the disease. The calcineurin inhibitors ciclosporin (4) and tacrolimus (5) are typical causative agents, but sirolimus (6) has also been associated with TMA. Graft outcomes have been reported as relatively poor in de novo disease, and treatment options limited to drug withdrawal and watchful waiting, or plasma exchange. Rejection rates in those needing CNI avoidance are high, and new therapies are urgently needed.

We report a single case of de novo drug-induced

Hindawi Publishing Corporation
Case Reports in Medicine
Volume 2013, Article ID 290254, 4 pages
http://dx.doi.org/10.1155/2013/290254

Case Report

Use of Belatacept as Alternative Immunosuppression in Three Renal Transplant Patients with *De Novo* Drug-Induced Thrombotic Microangiopathy

Federico Cicora,[1,2] Marta Paz,[1] Fernando Mos,[1] and Javier Roberti[2]

[1] *Renal Transplantation, Hospital Italiano, Presidente Perón 4190, C1181ACT Buenos Aires, Argentina*
[2] *Foundation for Research and Assistance in Renal Disease (FIMER), Calle 509 No. 1913 CP B1902FYU, Gonnet, Buenos Aires, Argentina*

Correspondence should be addressed to Javier Roberti, javierroberti@gmail.com

Received 14 June 2013; Revised 9 September 2013; Accepted 15 September 2013

Academic Editor: Simin Goral

Thrombotic microangiopathy (TMA), a severe complication of renal transplantation, is a pathological process involving microvascular occlusion, thrombocytopenia, and microangiopathic hemolytic anemia. It generally appears within the first weeks after transplantation, when immunosuppressive drugs are used at high doses. *De novo* TMA may also be drug-induced when calcineurin inhibitors or proliferation signal inhibitors are used. We report three cases of late-onset drug-induced TMA in renal transplant patients who were managed by replacing calcineurin inhibitors or proliferation signal inhibitors with belatacept, a primary maintenance immunosuppressive drug, which blocks the CD28 costimulation pathway, preventing the activation of T lymphocytes. To identify the cause of TMA, we ruled out HUS, hepatitis C serology, HIV serology, parvovirus B19, cytomegalovirus, anti-HLA antibodies, and prolonged activated partial thromboplastin time. We suspect that the TMA was caused by the calcineurin inhibitors or proliferation signal inhibitors. Belatacept treatment was initiated at a dose of 10 mg/kg on days 1, 5, 14, 28, 60, and 90; maintenance treatment was 5 mg/kg once a month for 1 year. Belatacept, in combination with other agents, prevented graft rejection in three patients.

American Journal of Transplantation 2011; 11: 2823–2827
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03595.x

Case Report

Eculizumab in Acute Recurrence of Thrombotic Microangiopathy After Renal Transplantation

K. Hadaya[a,b], S. Ferrari-Lacraz[c,d], D. Fumeaux[a], F. Boehlen[a], C. Toso[b,e], S. Wolf[f], P-Y. Martin[a] and J. Villard[c,d,*]

[a] *Division of Nephrology,* [b] *Division of Transplantation, Transplantation Immunology Unit,* [c] *Transplantation Immunology Unit, Division of Immunology and Allergy,* [d] *Division of Laboratory Medicine,* [e] *Division of Angiology and Hemostasis, and* [f] *Division of Pathology, Geneva University Hospital and Medical School, Geneva, Switzerland*

[*] *Corresponding author: Jean Villard, Jean.Villard@hcuge.ch*

Renal thrombotic microangiopathy (TMA) is a severe complication of systemic lupus erythematosus (SLE), which is associated with the presence of antiphospholipid (aPL) antibodies. In its most fulminant form, TMA leads to a rapid and irreversible end-stage renal failure. Eculizumab, an anti-C5 monoclonal antibody, is a novel therapy of choice for patients with paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome. Here, we report the case of a 27-year-old woman, known for SLE and end-stage renal disease due to fulminant TMA. Both aPL antibodies and antinucleosome antibodies were positive. The patient underwent a living-related kidney transplantation with immediate production of urine. Although serum creatinine was remaining high, a graft biopsy, performed on day 6, demonstrated a TMA recurrence. Despite a treatment with plasma exchange, the situation got worse and dialysis was started. Eculizumab treatment was subsequently administered and renal function improved rapidly. Three months after transplantation, serum creatinine was at 100 μmol/L, without proteinuria. This case illustrates the benefit of eculizumab therapy in a fulminant recurrence of TMA after kidney transplantation, resistant to classical therapy.

Received 26 April 2011, revised 08 June 2011 and accepted for publication 01 July 2011

Introduction

The renal involvement of the antiphospholipid syndrome (APS), also known as APS nephropathy, is characterized by renal artery and/or vein thromboses, renal infarction and/or allograft thrombosis after kidney transplantation (1,2). The intrarenal vascular lesions have been more specifically defined and include the thrombotic microangiopathy (TMA) and more chronic lesions such as fibrous intimal hyperplasia (FIH) and focal cortical atrophy (FCA; 3). When APS is associated with systemic lupus erythematosus (SLE), the TMA lesions are predominant, but FIH and FCA can also be found in addition to the classical lupus nephritis. Interestingly, no significant association has been demonstrated between APS nephropathy and the WHO class of lupus glomerulopathy (1,3). TMA in patients with SLE is frequently associated with bad renal outcomes (2) and its most fulminant form, combining TMA and the presence of antiphospholipid (aPL) antibodies, rapidly leads to irreversible end-stage renal failure (2).

In kidney transplantation, the significance of aPL antibodies on short- and long-term allograft survival and function has been analyzed in two studies. Forman et al. (4) have demonstrated that the presence of pretransplant anticardiolipin antibody does not impact post-transplant kidney function. However, they suggested that more research was required to address the significance of other aPL antibodies. More recently, Canaud et al. (5) demonstrated that the presence of lupus anticoagulant in kidney transplant recipients was associated with severe vascular lesions and poor functional outcome, especially in patients with APS.

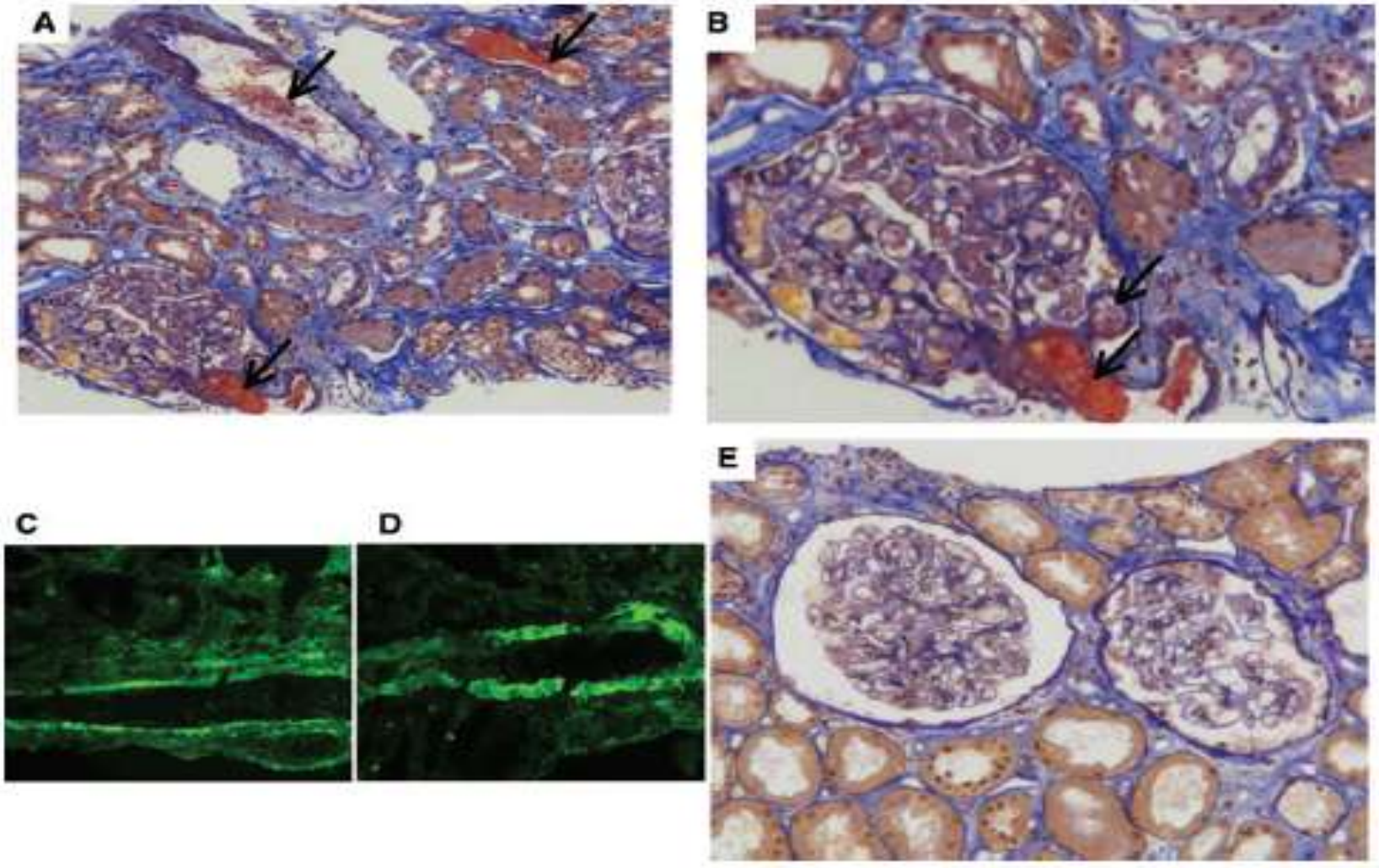


Figure 1: Histology of renal thrombotic microangiopathy (TMA) after transplantation. (A) Florid TMA with fibrin thrombi in arterioles at the glomerular vascular pole (black arrows) on day 6 posttransplantation. Thrombotic lesions are also observed in two interlobular arteries. Trichrome staining, original magnification: 120×. No evidence of cellular and antibody-mediated rejection was detected (left). (B) Enlargement of (A) showing TMA with fibrin thrombi at the glomerular vascular pole (black arrows). (C) Immunofluorescence shows moderate staining for C 5b-9 along and within the arterial walls. (D) Immunofluorescence shows moderate staining for C3 along and within the arterial walls. (E) Complete resolution of the glomerular lesions without sequel 3 months after TMA recurrence posttransplantation and eculizumab therapy. Trichrome staining, original magnification: 120× (right).

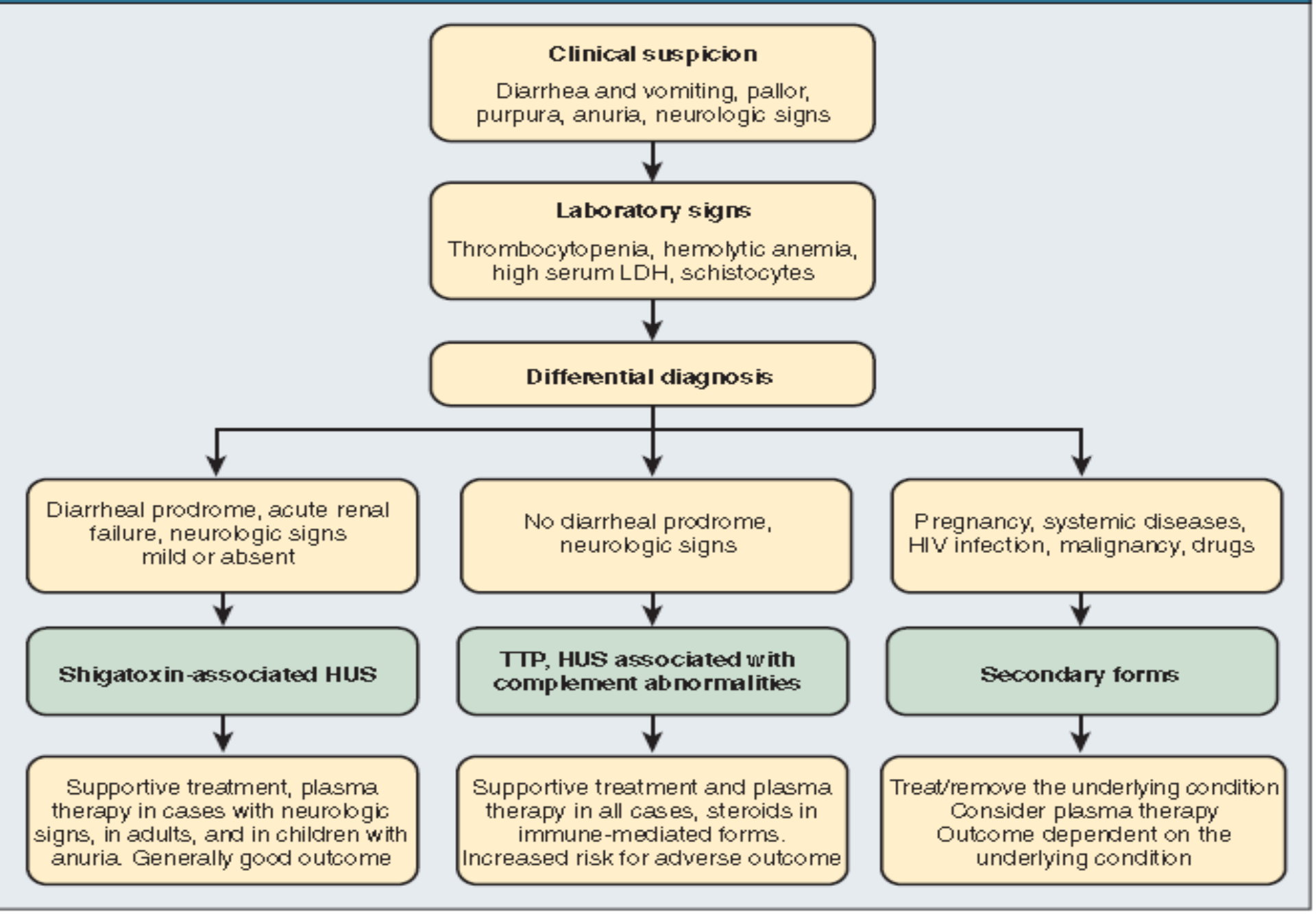
- patients at high risk of TMA recurrence should initially avoid those immunosuppressive drugs (CNI, mTOR antagonists and OKT3) that may enhance the development of TMA.
- A possible strategy may consist in an induction therapy with an anti-CD25 monoclonal antibody associated with mycophenolic acid and corticosteroids.
- In case of recurrence, plasma exchange twice a week and i.v. immunoglobulins (0.4 g/kg body weight) should be administered until remission.
- If there is no response,rituximab (375 mg/m2 weekly for 2–4 administrations)may be attempted.

Thanks

Prof. Mohamed Sobh

Prof. of Nephrology & Director of Medical Experimental Research Center

Differential Diagnosis of Thrombotic Microangiopathies



Specific Therapies Used in Thrombotic Microangiopathy, Doses, Modalities of Administration, and Effectiveness

Therapy	Dosing	Modality of Administration	Efficacy
Antiplatelet agents			
Aspirin	325–1300 mg/day	Oral	Anecdoctal reports in TTP forms
Dipyridamole	400–600 mg/day	Oral	" "
Dextran 70	500 mg twice/day	Intravenous injection	" "
Prostacyclin	4–20 ng/kg/min	Continuous intravenous infusion	" "
Antithrombotic agents			
Heparin	5000 U	Pulse intravenous injection	Anecdoctal reports in HUS
	750–1000 U/hour	Continuous intravenous infusion	
Streptokinase	250,000 U	Pulse intravenous injection	" "
	100,000 U/hour	Continuous intravenous infusion	
Antioxidant agents			
Vitamin E	1000 mg/m^2/day	Oral	Anecdoctal reports in HUS
Immunosuppressive agents			
Prednisone / prednisolone	200 mg tapered to 60 mg/day Then 5-mg reduction per week	Intravenous or oral during active disease then continue with oral	Probably indicated in patients with TTP and anti-ADAMTS13 autoantibodies or in aHUS with anti-factor H autoantibodies and in forms associated with autoimmune diseases
Immunoglobulins	400 mg/kg/day	Intravenous infusion	
Vincristine	1.4 mg/m^2 on day 1	Intravenous injection	
	1 mg every 4 days Intravenous	Intravenous injection up to 4 doses	
Rituximab	375 mg/m^2/week for 4 weeks	Intravenous injection	
Fresh frozen plasma			
Exchange	1–2 plasma volumes/day	Intravenous infusion, up to remission	First-line therapy
Infusion	20–30 ml/kg on day 1	Intravenous Infusion	First-line therapy if plasma
	10–20 ml/kg/day thereafter	Intravenous infusion up to remission	exchange is not available
Cryosupernatant	See plasma infusion/exchange	See plasma infusion/exchange	Instead of whole plasma in case of plasma resistance or sensitization
Solvent detergent treated	See plasma infusion/exchange	See plasma infusion/exchange	Instead of whole plasma to limit the risk of infections
Others			
Liver transplant			To cure complement genetic defect (factor H)
Eculizumab	600 mg weekly for the first 4 weeks	Intravenous infusion	Reported efficacy in cases of aHUS due to factor H mutations and of aHUS recurrence after kidney transplant
	900 mg every 14 days thereafter up to 6 months		

Recommendations in 2007

Recommendations in 2007 can reasonably be as follows:

1) All patients with aHUS, and also patients with an uncertain diagnosis of D+/STEC + HUS, should undergo complement factors determination (C3, CFH, IF, BF, and MCP expression), screening for anti-CFH antibodies, and genotyping for CFH, CFH-linked genes, IF, MCP, BF, and C3 before transplantation

2) Living-related donors should not be recommended for aHUS patients whatever their genetic background. Nevertheless, when live related transplantation is the only possible option and the donor wishes to proceed his project, complete genotyping of the related donor should be performed. If the donor has neither the mutation of his related recipient nor any other mutation, he must be informed that there remains a possibility that he might have some unknown risk factor of developing HUS after kidney donation.

3) Patients with MCP mutation can reasonably undergo transplantation. For the other patients, the decision of kidney transplantation is difficult.

4) For patients with CFH mutation, three options are presently available (Fig. 3):

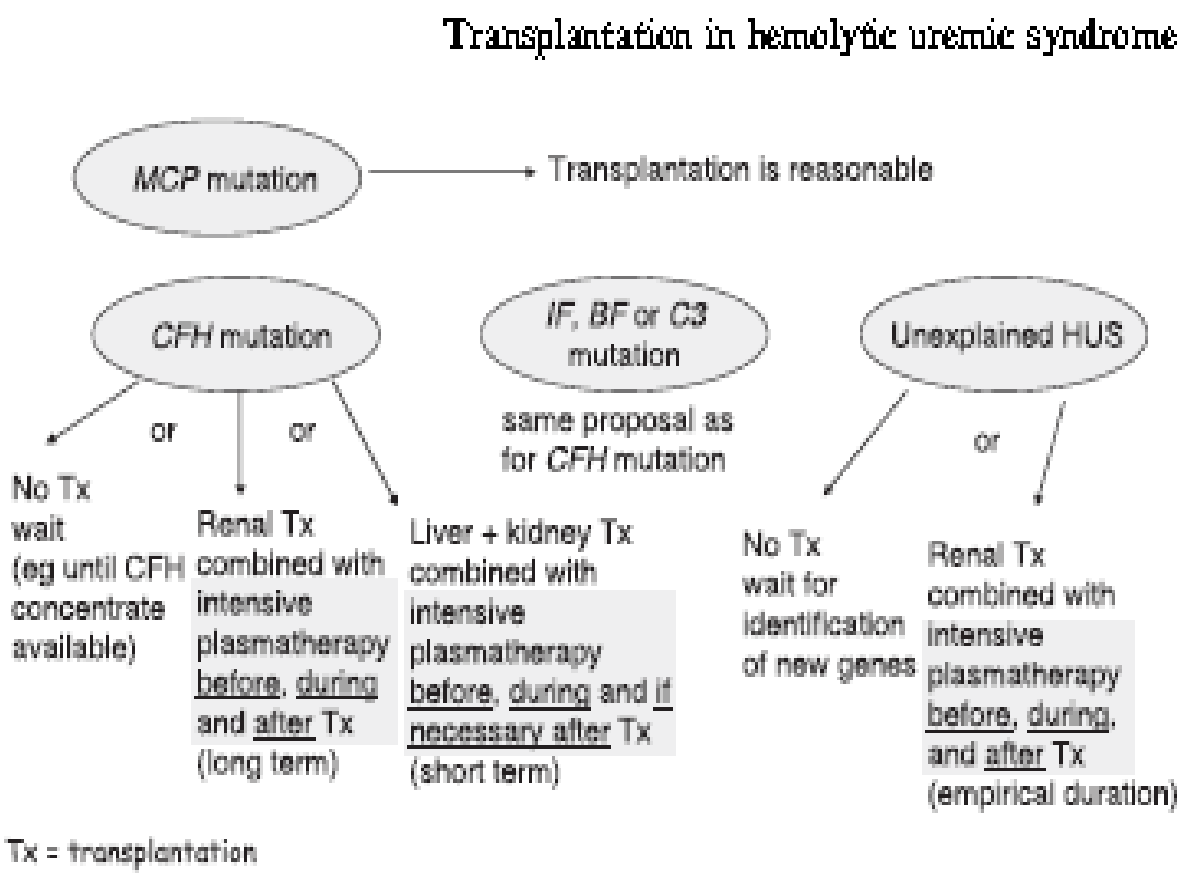
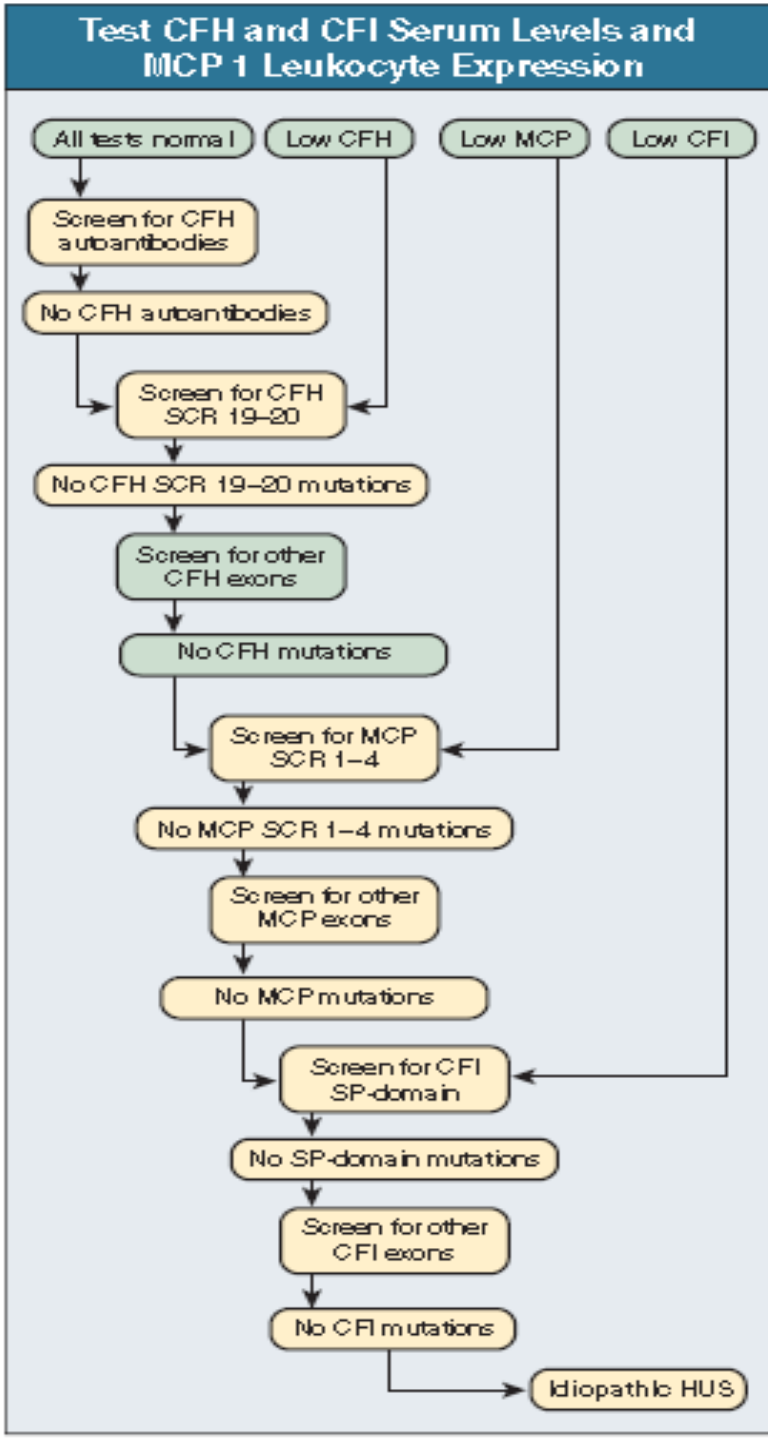


Fig. 3. Renal transplantation in aHus patients: therapeutic options in 2007.

Specific Therapies Used in Thrombotic Microangiopathy, Doses, Modalities of Administration, and Effectiveness

Therapy	Dosing	Modality of Administration	Efficacy
Antiplatelet agents			
Aspirin	325–1300 mg/day	Oral	Anecdoctal reports in TTP forms
Dipyridamole	400–600 mg/day	Oral	" "
Dextran 70	500 mg twice/day	Intravenous injection	" "
Prostacyclin	4–20 ng/kg/min	Continuous intravenous infusion	" "
Antithrombotic agents			
Heparin	5000 U 750–1000 U/hour	Pulse intravenous injection Continuous intravenous infusion	Anecdoctal reports in HUS
Streptokinase	250,000 U 100,000 U/hour	Pulse intravenous injection Continuous intravenous infusion	" "
Antioxidant agents			
Vitamin E	1000 mg/m^2/day	Oral	Anecdoctal reports in HUS
Immunosuppressive agents			
Prednisone / prednisolone	200 mg tapered to 60 mg/day Then 5-mg reduction per week	Intravenous or oral during active disease then continue with oral	Probably indicated in patients with TTP and anti-ADAMTS13 autoantibodies or in aHUS with anti-factor H autoantibodies and in forms associated with autoimmune diseases
Immunoglobulins	400 mg/kg/day	Intravenous infusion	
Vincristine	1.4 mg/m^2 on day 1 1 mg every 4 days	Intravenous injection Intravenous injection up to 4 doses	
Rituximab	375 mg/m^2/week for 4 weeks	Intravenous injection	
Fresh frozen plasma			
Exchange	1–2 plasma volumes/day	Intravenous infusion, up to remission	First-line therapy
Infusion	20–30 ml/kg on day 1 10–20 ml/kg/day thereafter	Intravenous Infusion Intravenous infusion up to remission	First-line therapy if plasma exchange is not available
Cryosupernatant	See plasma infusion/exchange	See plasma infusion/exchange	Instead of whole plasma in case of plasma resistance or sensitization
Solvent detergent treated	See plasma infusion/exchange	See plasma infusion/exchange	Instead of whole plasma to limit the risk of infections
Others			
Liver transplant			To cure complement genetic defect (factor H)
Eculizumab	600 mg weekly for the first 4 weeks 900 mg every 14 days thereafter up to 6 months	Intravenous infusion	Reported efficacy in cases of aHUS due to factor H mutations and of aHUS recurrence after kidney transplant



Flow diagram of the steps suggested optimize the cost-effectiveness of screening for genetic defects in patients with non–Stx-associated HUS and genetically determined abnormalities in complement regulatory proteins. CFH, complement factor H; CFI, complement factor I; HUS, hemolytic-uremic syndrome; MCP, membrane cofactor protein; SCR, short consensus repeats.

- At least 80% of childhood, but no more than 5% of adult HUS is D+HUS.
- After exposure to Stx-E coli, 3 to 9% in sporadic cases,and up to 20% in epidemic forms, develop HUS .
- Larger amount of toxin, treatment with antimicrobial agents, and/or a profound inflammatory response, all favor the onset

  of full-blown HUS.
- Toxin-laden neutrophils transmit the Stx to the kidneys where it is

  delivered to high-affinity glycolipid receptor,globotriacylceramide (Gb3), expressed on glomerular endothelial, tubular and mesangial

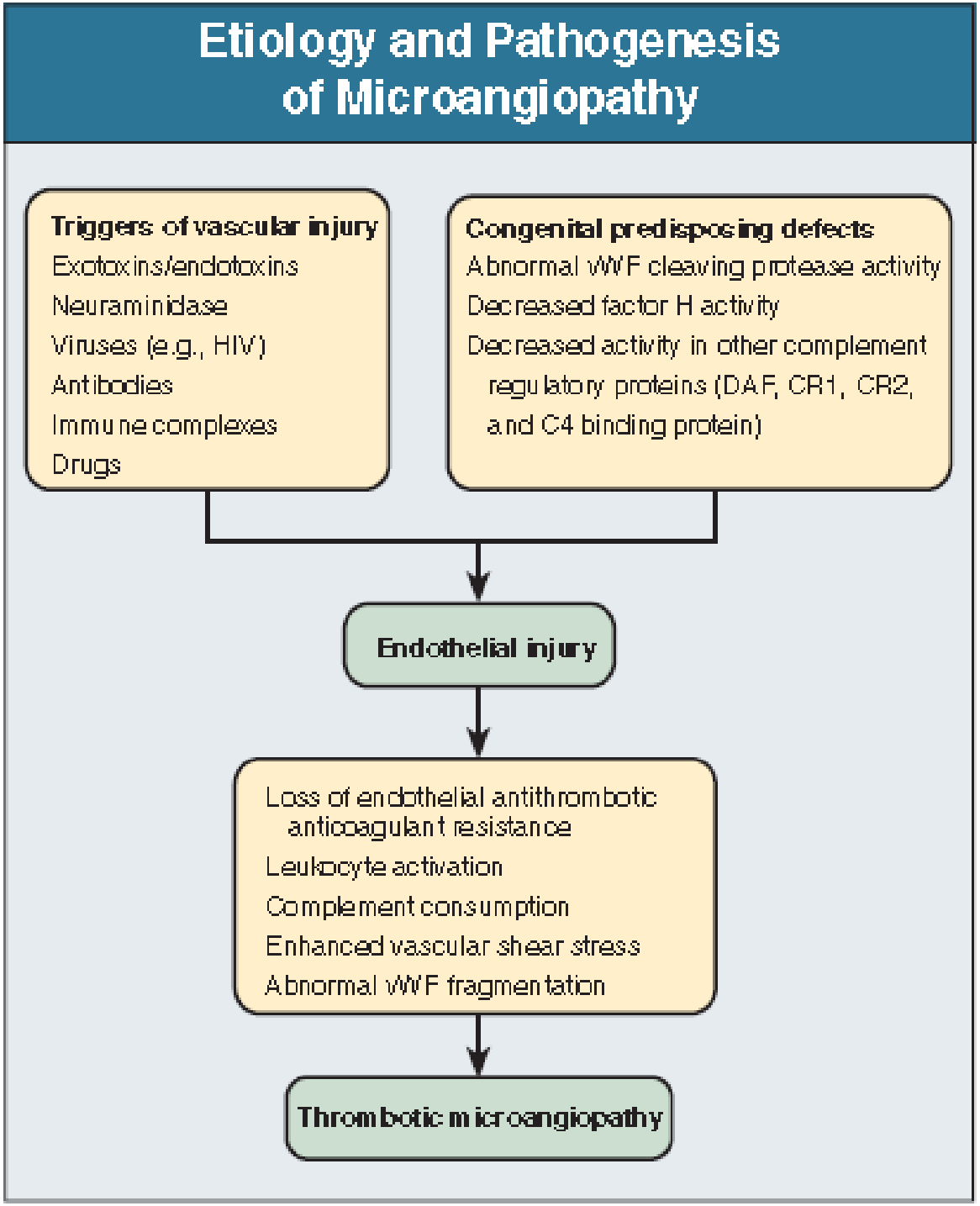
  cells.
- The prevalence of these receptors in the kidney is the biochemical basis for the preferential renal involvement in HUS.
- After internalization, this toxin induces endothelial damage (apoptosis, and necrosis), increases adhesion properties and increases von Willebrand Factor (VWF) secretion.

- Non-Stx- HUS is less common than Stx-HUS and accounts for only 5-10% of all cases of HUS.
- Non-Stx-HUS can occur sporadically or in families and most frequently seen in adults.
- A wide variety of triggering factors have been identified for the sporadic form of D-HUS, including:
- bacterial and viral infections, pregnancy, scleroderma,systemic lupus erythematosus (SLE),anti-phospholipid antibody disease and a long list of drugs including mitomycin, cysplatin,bleomycin, gemcitabin, cyclosporin, tacrolimus,OKT3, quinidine, ticlopedin, clopedigrel,INF-alfa.
- In approximately 50% of sporadic, non-Stx-HUS (idiopathic HUS), no

clear triggering factor can be found.

- Familial forms account for less than 3% of all cases of HUS; both dominant and recessive forms have been reported.
- Familial HUS and sporadic non-Stx-HUS may be caused by genetic abnormalities of proteins involved in the regulation of complement activation.

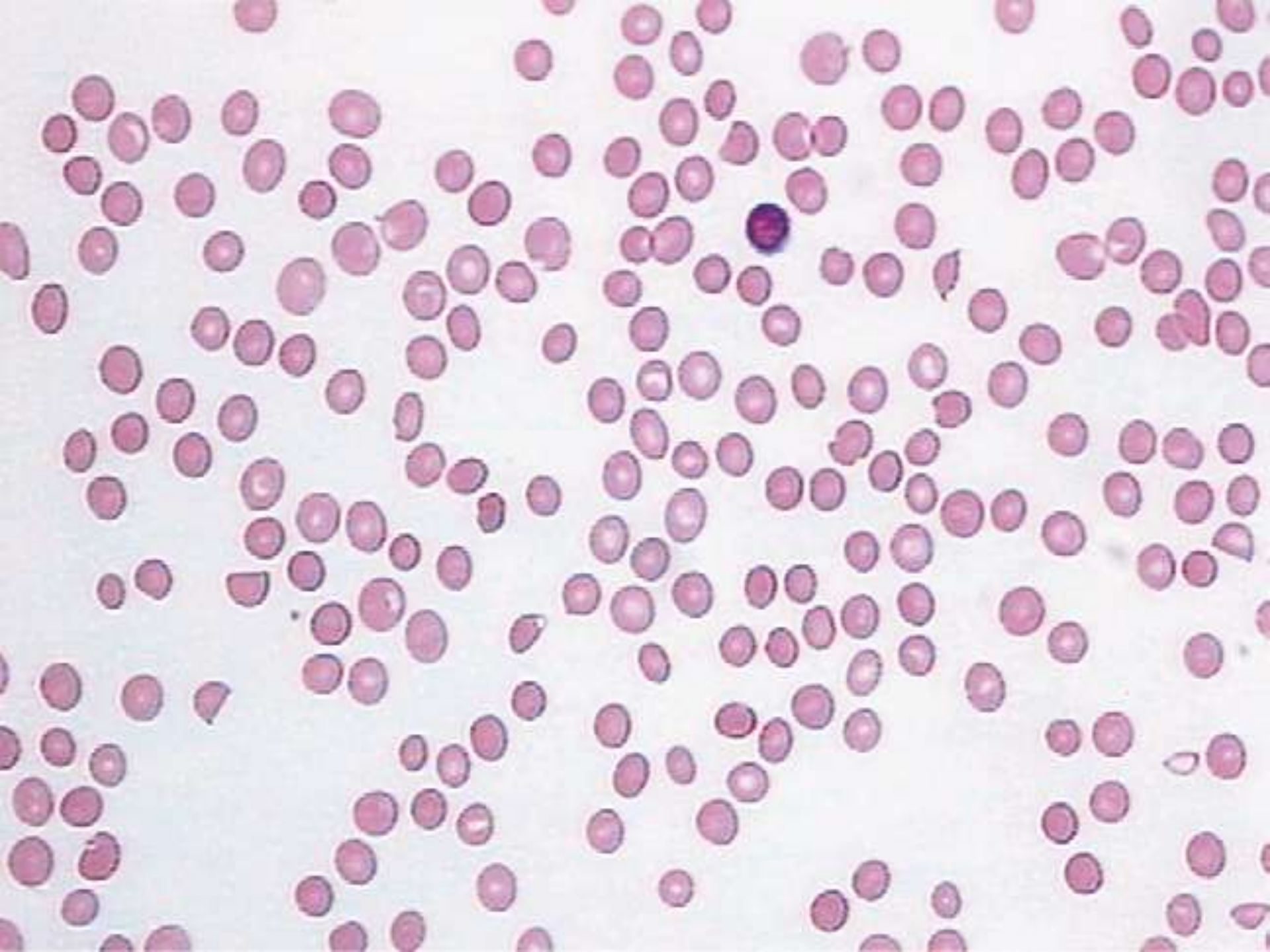
- Injury to the endothelial cell is the central and likely inciting factor in the sequence of events leading to TMA.
- Loss of physiologic thromboresistance, leukocyte adhesion to damaged endothelium, complement consumption, abnormal von Willebrand factor (vWF) release and fragmentation, and increased vascular shear stress may then sustain and amplify the microangiopathic process.


Etiology and Pathogenesis of Microangiopathy
Triggers of vascular injury
Exotoxins/endotoxins
Neuraminidase
Viruses (e.g., HIV)
Antibodies
Immune complexes
Drugs
Congenital predisposing defects
Abnormal vWF cleaving protease activity
Decreased factor H activity
Decreased activity in other complement regulatory proteins (DAF, CR1, CR2, and C4 binding protein)
Endothelial injury
Loss of endothelial antithrombotic anticoagulant resistance
Leukocyte activation
Complement consumption
Enhanced vascular shear stress
Abnormal vWF fragmentation
Thrombotic microangiopathy

CLINICAL AND LABORATORY SIGNS

- TMA is characterized by thrombocytopenia (often with purpura but rarely with severe bleeding),
- Microangiopathic hemolytic anemia,
- AKI that may be associated with anuria, neurologic deficits,and fever.
- Thrombocytopenia and hemolytic anemia are the key laboratory abnormalities.
- Thrombocytopenia is caused by platelet aggregation in the microcirculation; hemolytic anemia is due to mechanical fragmentation of erythrocytes during their passage through the narrowed vessels.
- Hyperbilirubinemia (mainly indirect), reticulocytosis, circulating free hemoglobin, and low haptoglobin levels are typical.

- The serum lactate dehydrogenase (LDH) level is extremely high, reflecting hemolysis but also, in some patients, diffuse tissue infarction.
- Platelet count and serum LDH level are useful parameters for both diagnosis and response to treatment.
- Fragmented red blood cells (schistocytes) with the typical appearance of a helmet in the peripheral smear and a negative Coombs test result (with the exception of neuraminidase-associated TMA) are needed to confirm the microangiopathic nature of hemolysis.



- There is often leukocytosis with a left shift in Shiga toxin (Stx)–associated HUS, whereas leukocytes are usually normal in atypical HUS (aHUS) and TTP.
- Prothrombin time and partial thromboplastin time, factor V, factor VIII, and fibrinogen are

DIFFERENTIAL DIAGNOSIS

- Differential diagnosis includes systemic vasculitis,hypertensive emergency, disseminated intravascular coagulation (DIC), and endemic Hantavirus infection.
- Other conditions that can cause an HUS-like picture include scleroderma and radiation

- The prognosis is good in the patients with predominant glomerular involvement, but it is more severe in those with predominant preglomerular injury.
- Focal segmental glomerulosclerosis (FSGS) may be a long-term sequela of acute cases of HUS and is usually seen in children with long-lasting hypertension and progressive chronic renal function deterioration.

- Thrombotic microangiopathy (TMA) is a histopathological term that defines glomerular, arteriolar or interlobular artery lesions, characterized by patchy distribution, with intimal cell proliferation, thickening and necrosis of the wall, thrombi and narrowed lumens.
- The severity of lesions is variable ranging from endothelial swelling to complete cortical necrosis.

- The constituents of arterial thrombi in TTP and HUS include platelet and VWF initially, and fibrinogen and thrombin at later stages.
- Sometimes, the histological findings are indistinguishable from malignant hypertension.
- Criteria for pathologic diagnosis of TMA, includes presence of one or more of the following findings:

  a) Arteriolar or arterial thrombi

  b) Occlusion of glomerular capillaries with amorphous material that correspond to sub-endothelial accumulation of electron lucent deposits.

  c) Severe arteriolar or arterial endothelial widening

- Interestingly, antimicrobial treatment could worsen the outcome of D+HUS and plasma exchange worsens the nuraminidase associated HUS.
- In resistant forms of HUS, removal of the kidney as a major site of augmented shear stress is followed by hematological and clinical remission.
- Splenectomy as a rescue therapy may serve in very selected cases of plasma exchange-resistant HUS, or recurrent TTP.
- Rituximab is a promising first-line immunosuppressive treatment in patients with acute refractory, and severe relapsing, TTP related to anti-ADAMTS13 antibodies.
- Anti-thrombotic or anti-platelet agents are not helpful.